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Light stability of molsidomine in infusion fluids

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Abstract—The influence of artificial light, daylight or stimulated sunlight on the stability of molsidomine was investigated. In static experiments an 80 $\mu g\ mL^{-1}$ solution of molsidomine in saline was stored in an unprotected infusion bag. During dynamic experiments the molsidomine solution (80 $\mu g\ mL^{-1}$) was dropped at 12·5 $mL\ h^{-1}$ from an unprotected infusion bag, from an infusion bag covered with aluminium-foil, or from an infusion bag protected with a UV-cover. Either unprotected infusion tubing or infusion tubing with a UV-filter were connected to the infusion bags. Static as well as dynamic experiments showed a half-life of about 20 min for the unprotected molsidomine solutions, when placed behind a window during a sunny day. Protection from light of the infusion bag but not of the infusion tubing had only a minor influence on the drug half-life. Protection of the infusion bag and the infusion tubing with a UV-filter increased the half-life to several days. These results confirm that both the infusion bag and the infusion tubing need adequate light protection during molsidomine administration.

In current clinical practice, antianginal drugs such as nitroglycerin and isosorbide dinitrate during the acute phase of myocardial infarct are often replaced by molsidomine. In addition to its vasodilating effect, molsidomine has anti-platelet aggregation properties and shows a lower tolerance than other anti-anginal drugs (Mukharljamov et al 1986). Apart from these pharmacological differences, some important physicochemical characteristics need to be considered. Nitroglycerin and isosorbide dinitrate are subject to adsorption and absorption to administration sets. This results in a decrease (up to 35%) of the amount of the drug available during the first 5 h of administration, depending on the polymer materials of the medical devices used during therapy.

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In this study the stability of molsidomine in adminstration sets was investigated. The leaflet of molsidomine i.v. ampoules (Corvaton, Therabel Pharma, Brussels, Belgium) recommends protection from light. As this advice is not always followed in daily clinical practice, the stability of molsidomine was compared in several experimental arrangements. The stability in unprotected, partially protected and UV-protected administration sets, exposed to different light sources, was compared. Preliminary data have already been presented (De Muynck et al 1992).

Materials and methods

Dilution and administration sets. For both static and dynamic experiments, molsidomine ampoules were diluted to a concentration of 80 $\mu g\ mL^{-1}$ in 50 mL saline (0·9% NaCl w/v) in polyvinylchloride (PVC) infusion bags (Viaflex, Lessines, Belgium). Static experiments were performed with unprotected infusion bags. Samples were taken every 10 min for 3 h, every hour over 10 h and after 24 h. In the dynamic experiments an unprotected infusion bag and an infusion bag covered with aluminium foil were connected to unprotected PVC infusion tubing (Shore A hardness 65, plasticizer: DEHP, Rehau, Rehau, Germany), whereas an infusion bag protected with a UV-cover (Sureset A261, Avon Medicals, Reddich, UK) was connected to

Table 1. Static experiments.

Light source	Light intensity and other specifications	Half-life (mean ± s.d.)
No light	0 lux 60°C###	> 3 days (1)
Fluorescent lamp	125 lux 2 m#	> 3 days (1)
Incandescent lamp	$1{\cdot}5 \times 10^5$ lux 20 cm	> 3 days (1)
Daylight (outside)	12·5 J cm^{-2} (sunny)	8 min (1)
Daylight (behind a window)	12·5 J cm^{-2} (sunny)	24 ± 6 min (3)
	5·1 J cm^{-2} (unsettled)	28 ± 1 min (3)
	3·9 J cm^{-2} (cloudy)	49 ± 1 min (3)
Simulated sunlight	$> 3{\cdot}5 \times 10^5$ lux 16 lamps## 0·5 m#	6 min (1)
	$3{\cdot}5 \times 10^5$ lux 16 lamps## 1 m#	11 min (1)
	$2{\cdot}5 \times 10^5$ lux 16 lamps## 2 m#	29 min (1)

Distance from the light source. ## Number of Ultra-Vitalux lamps. ### Temperature of the infusion bag.

Table 2. Dynamic experiments.

Light source light intensity and other specifications	Protection Bag	Protection Tubing	Half-life (mean ± s.d.) (n)
Fluorescent lamp 125 lux 2 m#	—	—	> 3 days (1)
	Aluminium foil	—	> 3 days (1)
	UV-filter	UV-filter	> 3 days (1)
Daylight (behind a window) 7·2 J cm^{-2} (outside)	—	No tubing	23 min (1)
(sunny)	—	—	17 min (1)
	Aluminium foil	—	17 min (1)
	UV-filter	UV-filter	> 1 day (1)
Daylight (behind a window) 11·9 J cm^{-2} (outside)	—	No tubing	26 min (1)
(sunny)	—	—	18 min (1)
	Aluminium foil	—	17 min (1)
	UV-filter	UV-filter	> 1 day (1)
Simulated sunlight $1{\cdot}75 \times 10^5$ lux 12 lamps## 2 m#	—	—	11 ± 0 min
	Alumium foil	—	20 ± 2 min (3)
	UV-filter	UV-filter	3 days (3)

Distance from the light source. ## Number of Ultra-Vitalux lamps.

a polyethylene infusion tubing with a UV-filter (Rehau, Germany). A flow rate of 12·5 mL h^{-1} was applied and samples were collected every 10 min over 3 h at the end of the infusion tubing.

Light sources. A static experiment where the solution was completely shielded from light, was performed at 60°C. For static as well as dynamic experiments different light sources and light intensities were used. The artificial light intensity was measured with a Lunasix (Gossen, Germany) lux meter (maximal value $3{\cdot}5 \times 10^5$ lux). The stability of a molsidomine solution in an unprotected infusion bag was tested after a 24-h exposure

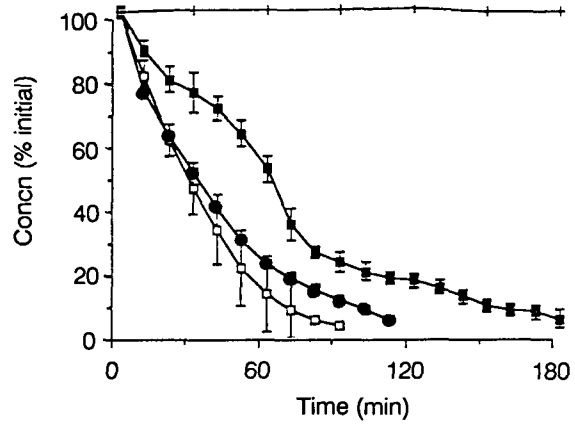

FIG. 1. Mean (±s.d.) molsidomine concentrations (% initial) as a function of time for static experiments with an unprotected infusion bag performed in a room protected from daylight (+) (n = 1) and performed behind the window in three different weather conditions (n = 3): 12·5 (□), 5·5 (●) and 3·9 lux (■).

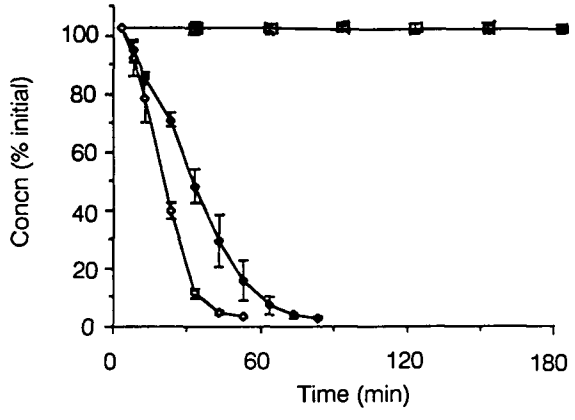

FIG. 2. Mean molsidomine concentrations (% initial) as a function of time for dynamic experiments, performed in simulated sunlight with an unprotected infusion bag and unprotected infusion tubing (◇), with an infusion bag, covered with aluminium foil and an unprotected infusion tubing (◆), with an infusion bag, covered with a UV-cover and an infusion tubing with UV-filter (□) (n = 1).

time at a 2-m distance from a fluorescence lamp (Acec, Brussels, Belgium) providing a light intensity of 125 lux or at a distance of 20 cm from an incandescent lamp (75 W, Osram, Zaventem, Belgium), providing a light intensity of $1{\cdot}5 \times 10^5$ lux. The samples were completely shielded from light and stored at 4°C. Static experiments were also performed, exposing the unprotected infusion bag to daylight outside or behind the window at the southern side of the building. The global radiation was measured as described by Crommelynck & Joukoff (1990). The light stability of molsidomine was also tested during exposure to light with a spectrum similar to sunlight. A set of 16 lamps (Ultra-Vitalux 300 W, Masson-Draguet, Wathier Braine, Belgium) mounted on 1 sq m were used during the static experiments at distances of 0·5, 1 and 2 m, resulting in a light intensity above $3{\cdot}5 \times 10^5$ lux, respectively. During the dynamic experiments 12 lamps were used at a distance of 2 m providing a light intensity of $1{\cdot}75 \times 10^5$ lux. As shown in Tables 1 and 2, each experimental procedure was repeated several times with one or three infusion sets.

Analysis. The stock solutions and the samples were protected from daylight, stored at 4°C and analysed by HPLC according to a method modified from Dutot et al (1990). The HPLC equipment consisted of a solvent pump (L 6000 pump, Merck-Hitachi, Tokyo, Japan), set at constant flow rate of 1 mL min^{-1}, a variable wavelength detector (L 4000 UV detector, Merck-Hitachi) set at 312 nm, a reversed phase column (Lichrospher 100 RP-18-5 μm, 125 mm × 4 mm, Merck, Darmstadt, Germany) and an automatic integrating system (D 2000 Chromato-Integrator, Merck-Hitachi). The eluent consisted of a 20/80 (v/v) ratio acetonitrile/citrate buffer (2·1%; w/v citric acid) (pH = 3·72). A linear interval ($r^2 = 0{\cdot}99996$) was observed between molsidomine (Sigma, St Louis, MO, USA) concentrations from 5 to 100 μg mL^{-1}. The coefficient of variation was 1·5%. The drug half-life was calculated from the individual curves. The dynamic experiments were performed over 3 h, half-lives longer than 1 or 3 days could therefore only be estimated and are presented as such in Tables 1 and 2.

Results

Static experiments. During one month storage at 4°C, after 24 h storage in an infusion bag in the dark at 60°C or after 24 h exposure to a fluorescence lamp or to an incandescent lamp no degradation was noticed. The half-life of a molsidomine solution exposed outside to daylight was only 8 min, whereas a simultaneous experiment behind the window resulted in a half-life of 24 min. Fig. 1 and Table 1 show the molsidomine half-life after exposure to daylight, behind a window, and under three different weather conditions. An inverse relation between the half-life and the light intensity was observed. A similar relation was observed when the molsidomine solution was exposed to simulated sunlight: a longer distance from the light source resulted in a lower light intensity and a longer half-life.

Dynamic experiments. As shown in the static experiment, no decrease in molsidomine concentration was noticed when the infusion bags and infusion tubings were kept in a room with only artificial light.

Exposure to daylight or simulated sunlight showed that protection of the infusion bag alone, resulted in a breakdown rate similar to that in the unprotected infusion bag (Fig. 2). Samples collected from the infusion bag exposed to daylight showed half-lives of about 25 min, whereas samples collected from an unprotected infusion tubing, connected to this infusion bag, showed a half-life of about 18 min. Exposure of the molsidomine solutions in the unprotected administration tubing to simulated sunlight over 12 h showed a degradation of at least 97·5%, whereas a degradation of less than 0·1% was noticed after UV-protection of the infusion bag and the infusion tubing.

Discussion

Admixing of a light protective agent such as toxerutin has been suggested in order to improve the light stability of tablets or solutions containing molsidomine (Voegele & Laudenbach 1985; Voegele et al 1986). In dynamic experiments, it was demonstrated that the protection of the infusion bag alone was insufficient to avoid degradation of molsidomine. When an infusion rate of 12·5 mL h^{-1} was used, the molsidomine solution was in the infusion tubing for over an hour. The long residence time in the infusion tubing and the exposure to light could explain the faster degradation in the unprotected infusion tubing as compared with the unprotected infusion bag.

The breakdown rate of molsidomine was related to the light intensity. In sunny weather conditions the half-life was shorter than in cloudy weather conditions. The dynamic and the static experiments with the unprotected infusion sets, placed behind the window, were performed once and three times, respectively, at 2 and 3 different weather conditions. The half-lives of between 17 and 50 min should, however, be interpreted in view of the prescribed continuous administration over 48 h. It was calculated that even at the longest half-life of 50 min, only 0·1% of the initial molsidomine concentration was left after 8 h of illumination. Several single experiments confirmed the light sensitivity of molsidomine, but in order to be able to compare the different arrangements, a standardized light source was preferable. To obtain breakdown kinetics similar to daylight, a preliminary static experiment was performed at different distances from simulated sunlight from Ultra-Vitalux lamps. The half-lives obtained after exposure to simulated sunlight were similar to those obtained in daylight. An inverse relation was found between the light intensity, the distance from the artificial sunlight source and the half-life. Molsidomine solutions exposed to artifical light, provided by fluorescent lamps or an incandescent lamp, remained stable even if the light intensity was as high as in daylight. A mean light intensity of $2{\cdot}8 \times 10^5$ lux was measured on the day with a mean global radiation of 12 J cm^{-2}. This indicated that the wavelength was a predominant factor in the degradation of molsidomine. The stability of the molsidomine solution protected by the UV-filters, eliminating mainly UV-light, supports this hypothesis. The slower degradation behind a window as compared with direct exposure might also be caused by the elimination of some of the UV-irradiation.

The observed decrease in molsidomine concentration was not due to the administration set nor was it caused by thermal degradation, as no degradation was observed when the molsidomine solution was kept in a room shielded from daylight or heated to 60°C. In view of the results obtained from this study the infusion bag as well as the infusion tubing should be protected from daylight during continuous molsidomine administration.

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